An Update
From the Food and Drug Administration
One Year on from the New Guidance

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Outline

- **A Brief Overview of the June 1999 Nasal BA/BE Guidance* ("New Guidance")**
- **Scientific and Regulatory Activities Following Release of the June 1999 Draft Guidance**

****Draft Guidance for Public Comments***

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A Brief Overview of the Draft Nasal BA/BE Guidance

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The Draft Guidance

Guidance for Industry:
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

- Applicable to Locally Acting Drug Products only
- Bioavailability (BA) Measurement
  - Predominantly non-comparative studies
- Bioequivalence (BE) Establishment
  - Comparative studies

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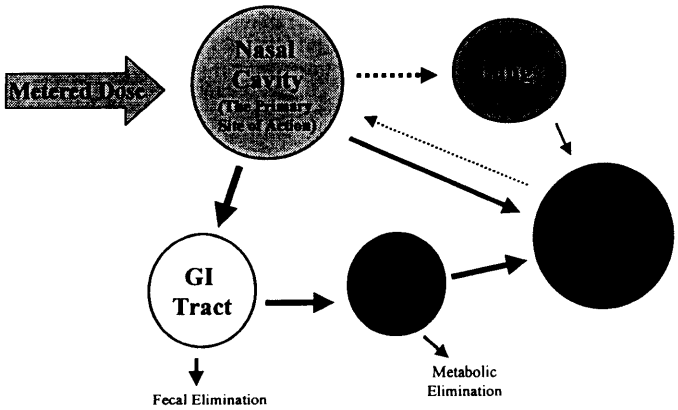
Approaches for Documentation of BA & BE

- In Vivo Studies in Humans Measuring Drug and/or Metabolite Concentrations in an Accessible Biological Fluid
- In Vivo Testing in Humans of an Acute Pharmacological Effect (Pharmacodynamic Effect Studies)
- Controlled Clinical Trials in Humans to Establish Safety and Efficacy
- In Vitro Methods

Complexity in Determination of BA/BE of Locally Acting Nasal Drug Products

Drug delivery to local site ~ Effectiveness
Drug Delivery to systemic circulation ~ safety (may also be effectiveness)
BA/BE based on systemic levels may or may not represent the local site BA/BE



Documentation of BE of Nasal Products

- **Suspensions**
  - Qualitative (Q1) and quantitative (Q2) sameness of product formulations
  - Device comparability
  - Demonstration of comparable performance of drug delivery devices (In vitro studies)
  - Demonstration of equivalent drug delivery to:
    - Local site of action (Clinical BE studies)
    - Systemic circulation (PK or PD studies)
- **Solutions**
  - Qualitative (Q1) and quantitative (Q2) sameness of product formulations
  - Device comparability
  - Demonstration of comparable performance of drug delivery devices (In vitro studies)

BE Studies for Nasal Products

- **Equivalent Drug Delivery to Local Site of action (Clinical End Point Studies)**
  - **Demonstration of dose response relationship**
    - **Second dose may differ by 2-4 fold**
    - **Lower dose may be below the labeled dose**
  - **Study Endpoints**
    - **Patient self-rated total nasal symptom scores (TNSS). Generally includes a composite score of runny nose, sneezing, nasal itching, and for drugs other than antihistamines and anticholinergics, congestion**
    - **Efficacy endpoint expressed as change from baseline**
    - **Incorporation of safety assessments**

BE Studies for Nasal Products

- **Clinical End Point Studies (Continued)**
  - **Study Designs: Randomized, double-blind, placebo-controlled parallel group studies**
  - **Study Type: Treatment not prophylactic**
  - **Subjects: Patients with a history of seasonal allergic rhinitis (SAR)**
  - **Exposure: Single dose (antihistamines) or short term multiple dose (corticosteroids) regimens**

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BE Studies for Nasal Products

- **Clinical End Point Studies (Continued)**
  - **Traditional Treatment Study:** Single-blind placebo lead-in period (1-14 days), two-week treatment duration. Nasal symptoms assessment twice daily and at the end of dosing interval. Safety measurements (adverse events reporting)
  - **Day(s) in the Park Study:** Baseline establishment, park exposure for specified periods over 1-2 days. Nasal symptoms assessment to characterize the onset of drug action and end-of-dosing interval efficacy. Safety assessment (adverse events reporting)
  - **EEU study:** Controlled indoor environment. Screening by repeated pretreatment exposure. EEU exposure to establish baseline. EEU exposure for specified periods over 1-2 days. Nasal symptoms assessment to characterize the onset of drug action and end-of-dosing interval efficacy. Safety assessment (adverse events reporting)

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BE Studies for Nasal Products

- **Systemic Exposure Studies**
  - **Study Design: Randomized, Two-way crossover**
  - **Subjects: Generally healthy volunteers**
  - **BE Metrics**
    - **PK (preferred): AUC and Cmax**
    - **PD (if PK is not feasible): Varies with the drug**

In Vitro BE Tests

- Dose or Spray Content
- Droplet Size Distribution
- Drug Particle & Drug Aggregate Size Distribution of Suspensions
- Spray pattern
- Plume geometry
- Priming and repriming
- Tail off

In Vitro BE Tests

- Compared With the In Vivo Tests
  - Relatively easy to perform
  - Do not require human volunteers
  - Higher precision due to lower variability
  - Greater sensitivity to detect small differences in product performance

In Vitro BE Tests

(Product Life Sectors* & Specific Recommendations)

- Dose or Spray Content (B, M & E for aerosols, B & E for sprays. Validated chromatographic/chemical Assay)
- Droplet Size Distribution (B, M & E. Three distances and three time delays. Laser diffraction or other established method)
- Drug Particle & Drug Aggregate Size Distribution of Suspensions
  - Using CI or MSLI (B & E. Validated chromatographic/chemical assay. Proper atomization chamber and flow rate)
  - Using Light Microscopy (B)
- Spray Pattern (B & E. Preferably drug or formulation-specific chromogenic reagent and automated quantitation method)
- Plume Geometry (B. At least three time delays. 0 and 90 degree rotation)
- Priming and Repriming (Validated assay. Consistency with labeling)
- Tail off (E. to depletion. Validated assay)

**Life Sectors: B - Beginning, M - Middle & E - End*

CI - Cascade Impactor. MSLI - Multistage Liquid Impinger

In Vitro BE Tests

(Study Measures & Data Evaluation Indices)

- Dose or Spray Content (Drug per single dose. Confidence intervals)
- Droplet Size Distribution (D50 and SPAN. Confidence intervals)
- Drug Particle & Drug Aggregate Size Distribution
  - Using CI or MSLI (Deposition profile over 3 groups. Confidence intervals)
  - Using Light Microscopy (Drug CMD & GSD for single particles, aggregate PSD. Supportive characterization)
- Spray Pattern (Dmax, Dmin and ovality ratio. Confidence Intervals)
- Plume Geometry (Plume length, width and cone angle. Supportive Characterization)
- Priming and Repriming (Drug per actuation. Confidence Intervals)
- Tail off (Drug per actuation. Qualitative Assessment)

D50 - Median Diameter, SPAN = (D90-D10)/D50. CMD - Count Median Diameter, GSD - Geometric Standard Deviation

Data Analysis

- Clinical BE Studies
  - Study design dependent. Analyses suitable for noncontinuous (categorical) data
- Systemic Exposure BE Studies (PK)
  - Two-one sided test (ANOVA)
- In Vitro BE Studies
  - Population BE analysis of non-profile data
  - Profile analysis of drug deposition (CI or MSLI studies)

Scientific and Regulatory Activities Following Release of the Draft Guidance for Public Comments

Post-Guidance Release Activities

- Comments to Docket 99D-1738
- OINDP[1] Subcommittee Meeting (26 April 2000)
- Non-FDA Technical Papers Submitted by ITFG/IPAC[2] Collaboration BA/BE Technical Team
- FDA/CDER Working Groups' Deliberations on In Vivo and In Vitro Testing, and Statistical Analyses of Study Data
- OINDP Subcommittee Report (ACPS[3] meeting, 15 November 2000)

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[1] Oral Inhalation and Nasal Drug Products. [2] Inhalation Technology Focus Group (ITFG)/ International Pharmaceutical Aerosol Consortium (IPAC). [3] ACPS - Advisory Committee for Pharmaceutical Science

Post-Guidance Release Activities:
Comments to Docket 99D-1738

- Fourteen (14) Firms and Organizations
- Comments Related to
  - Clinical BE Studies
  - Systemic Exposure Studies
  - In Vitro Performance Tests
  - Data Analysis

Post-Guidance Release Activities:
OINDP Subcommittee Meeting (26 April 2000)

- Participants
  - Some ACPS members
  - Academicians
  - Industry (Drug Manufacturers and CROs)
  - Agency Scientists
- Agenda
  - CMC: Content Uniformity
  - In Vitro BA/BE Testing
    - Analysis of Cascade Impactor data
    - In vitro tests for DPI performance/comparability
  - In Vivo BA/BE Testing
    - Clinical studies for local delivery of nasal aerosols and sprays
    - Clinical studies for local delivery of orally inhaled nasal aerosols
  - Open Public Hearing
  - Question to the Subcommittee

Post-Guidance Release Activities:
Non-FDA ITFG/IPAC Technical Papers

- **Initial Assessment of the ITGF/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration (31 July 2000)**
  - Deals with the CMC specifications, not BA/BE testing
- **Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITGF/IPAC Collaboration (29 August 2000)**
  - Deals with the CMC specifications for "Mass Balance" in particle size determinations, not BA/BE testing
- **Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at the 26 April 2000 OINDP Advisory Subcommittee meeting (30 August 2000)**
- **Review of In Vivo and In Vitro Tests in the FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs (30 August 2000)**

Post-Guidance Release Activities:
In Vivo BE Tests*

- General Comments
  - Clinical efficacy studies alone cannot establish BE
  - Systemic PK/PD studies establish systemic exposure, not local delivery
  - Lung deposition studies do not replace studies required to demonstrate local delivery
  - Possible reduction of testing requirements with validated models

**Public Comments Received by the Agency*

Post-Guidance Release Activities:
Clinical Studies*

- Demonstration of Dose Response
  - Necessity vs. Feasibility
- Placebo
  - Lead-in or a randomized treatment-arm
- Number of Clinical Studies
  - All three studies or fewer
- Extension of BE based on SAR study to PAR
- TNSS
  - Instantaneous or Reflective, or both
- Treatment Evaluation
  - Twice daily vs. once daily

*Public Comments Received by the Agency

Post-Guidance Release Activities:
Systemic Exposure Studies*

- Feasibility of PK Study
  - Pilot study
  - Number of doses and dosing intervals
  - Assay sensitivity
- HPA Axis Suppression Study
  - Sensitivity
  - Model validity

*Public Comments Received by the Agency

Post-Guidance Release Activities:
In Vitro BE Tests*

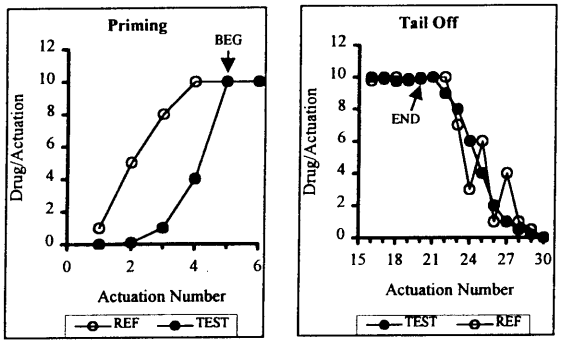
- General Comments
  - Significance of the formulation Q1 and Q2 sameness in the presence of an acceptable clinical study
  - 30 canisters/bottles (10 from each lot)
  - Need for automated actuations devices
  - Blinding in the presence of automated actuation devices
  - Number of actuations to prime
  - Significance of tail off data
  - What is "supportive characterization"?
  - Relative sensitivity of in vitro and in vivo tests to detect different product performances
  - Distinction between the nasal solution and suspension products with regard to in vivo BE study requirements
  - Consistency of the Guidance with the CMC guidance

**Public Comments Received by the Agency*

CMC Test	In Vitro BE Test
Noncomparative	Comparative
Focuses on setting specifications based on the identity, purity and potency of the drug product	Focuses on drug release from drug product
Specifications consist of a test, an analytical procedure, and an acceptance criterion	Equivalence comparisons may be based on criterion for sameness incorporating mean performance and variability
Specifications are based on manufacturing experience, drug development data, pharmaceutical standards, and accelerated stability studies.	BE limits may be based on mean performance and variability of test and reference products
Specifications assure product quality at release and during shelf life	BE limits assure equivalent product performance in drug delivery

Post-Guidance Release Activities:
In Vitro BE Tests (Continued)

- Priming and Tail Off Characteristics
  - **Priming: Primed at the first full medication dose (Based on the RLD labeling)**
  - **Tail Off: Characterizes drug delivery following labeled number of doses. The tail off is no more erratic than that of the RLD**



The graphs are based on hypothetical data for illustration only

Post-Guidance Release Activities:
In Vitro BE Tests* (Continued)

- Dose or Spray Content Uniformity
  - Number of sprays per nostril vs. Minimum dose
  - Chemical assay vs. gravimetric measurements
  - Stability indicating assay
  - Specification limits (85-115, 80-120 and 75-125)
- Droplet Size Distribution by Laser Diffraction
  - Significance of three delay times and three distances
  - Obscuration levels
  - Representative computer printouts
  - Variability of D50 and SPAN

**Public Comments Received by the Agency*

Post-Guidance Release Activities:
In Vitro BE Tests* (Continued)

- Drug Particle and Drug Aggregate Size Distribution
  - Feasibility of determination of PSD of drug substance in the aqueous nasal suspension sprays
  - Suitability for nasal products of CI & MSLI optimized for oral inhalation products
    - Suitability of the USP throat for nasal drug products
    - Flow rate
  - Distinction between "drug" and "drug aggregate"

**Public Comments Received by the Agency*

Post-Guidance Release Activities:
In Vitro BE Tests* (Continued)

- Spray Pattern
  - Significance of three distances

  - Number of actuations (single, multiple or minimum dose)
  - Drug specific visualization
  - Representative photographs
  - Confidence intervals on "ovality ratio", due to high variability on "Dmin" and "Dmax"

**Public Comments Received by the Agency*

Post-Guidance Release Activities:
In Vitro BE Tests* (Continued)

- Plume Geometry
  - Significance of three distances
  - Significance of three time delays
  - Significance of two views (0° and 90°)
  - Reproducibility of plume angle beyond the initial formation
  - Representative photographs
  - Confidence intervals on "ovality ratio", due to high variability on "Dmin" and "Dmax"

Public Comments Received by the Agency

Post-Guidance Release Activities:
Data Evaluation

- Within unit (canister/bottle) variability
- Within-lot variability
- Between-lot variability
- Total variability
- Significance of distances, time delays, obscuration etc. (where applicable)
- Ratio of means

Post-Guidance Release Activities:
Data Analysis

- Simulation of Unit Dose and Cascade Impactor Data and Development of Statistical Methods for
  - Profile-based data (Yi Tsong, QMRS, FDA)
    - A Chi square-based approach
    - Takes into consideration the relative variability of T and R
  - Non-profile data (Walter Hauck, Thomas Jefferson University)
    - A population BE approach
    - Takes into consideration the relative variability of T and R
    - Scaling of upper BE limit based of variability of R
      - Scaling variance ($Sigma_T^2$)
      - Variance term offset ($Epsilon_P$)

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Wallace Adams, Ph.D.

Members of the CDER Technical Committee for Oral Inhalation and Nasal Drug Products

Walter Hauck, Ph.D. (Thomas Jefferson University)

Oral Inhalation and Nasal Drug Products (OINDP) Committee*
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Comparative Systemic Absorption (Safety)	Debra Birenbaum Dale Conner Gur Jai Pal Singh	Tien-Mien (Albert) Chen Robert Meyer Sandra Saurez

** Part of the CDER BCC and CMC CC** Locally Acting Drug Products Technical Committee*

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FDA Guidances Related to the Draft Nasal BA/BE Guidance

- Guidance for Industry - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Control Documentation(October 1998) - *Draft*
- Guidance for Industry - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products: Chemistry, Manufacturing, and Control Documentation (May 1999) - *Draft*
- Guidance for Industry - Allergic Rhinitis: Clinical Development Programs for Drug Products (April 1999) - *Draft*
- Guidance for Industry - Points to Consider: Clinical Development Programs for MDI and DPI Products (September 1994)
- Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (October 2000)

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